Prognostic Impact of Adjuvant Chemotherapy after Hepatic Resection for Synchronous and Early Metachronous Colorectal Liver Metastases

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Keywords

Colorectal liver metastases · Adjuvant chemotherapy · Disease-free interval

Abstract

Background: Although the usefulness of adjuvant chemotherapy has been established in the treatment for stages II/III colorectal cancer, its prognostic advantage for colorectal liver metastases (CLM) remains controversial. **Methods:** Two hundred and nine patients who underwent curative resection for CLM were reviewed. The potential advantage of adjuvant chemotherapy was investigated in 3 groups stratified by disease-free interval (DFI): synchronous CLM (S-CLM), early metachronous CLM (EM-CLM, DFI ≤ 1 year), and late metachronous CLM (LM-CLM, DFI > 1 year). **Results:** Of the 105 patients who underwent adjuvant chemotherapy after surgery, 47 received uracil-tegafur and leucovorin (UFT/LV) while 58 received the oxaliplatin-based regimen. Five-year recurrence-free survival (RFS) rates in patients with/without adjuvant chemotherapy were 32.8/11.2% in S-CLM ($p = 0.002$), 43.7/15.2% in EM-CLM ($p = 0.002$), 44.1/29.6% in LM-CLM ($p = 0.163$), respectively. Five-year overall survival (OS) rates were 77.9/44.5% in S-CLM ($p = 0.021$), 81.5/39.5% in EM-CLM ($p = 0.015$), 76.1/65.4% in LM-CLM ($p = 0.411$), respectively. Multivariate analyses in S-CLM and EM-CLM indicated that

adjuvant chemotherapy is correlated with better RFS and OS irrespective of the regimens, while the incidence of severe adverse event was significantly different between UFT/LV and oxaliplatin (6.8 vs. 50.9%, $p < 0.0001$). **Conclusion:** Adjuvant chemotherapy might improve the clinical outcomes in S-CLM and EM-CLM. UFT/LV might be a choice for CLM in adjuvant settings in selected patients.

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Introduction

Hepatic resection is acknowledged to be the most effective treatment for patients with colorectal liver metastases (CLM) [1, 2]. With recent dramatic advancements in systemic therapies for colorectal cancer (CRC), it has been reported that chemotherapy followed by an aggressive surgical approach as a part of multidisciplinary treatment may improve the long-term outcomes in selected patients with CLM [2–4]. However, the use of adjuvant systemic therapy for CLMs remains controversial.

As for primary CRC, many trials have revealed that adjuvant chemotherapy after surgery improves the outcome of patients with stages II or III CRC and its prognostic benefit has been established. For patients with CLM, however, only limited evidence is available. To

date, several studies have reported that adjuvant chemotherapy prolonged recurrence-free survival (RFS) after resection of CLM using 5-fluorouracil with leucovorin (5-FU/LV) [5], FOLFOX [4], or uracil-tegafur (UFT; Taiho Pharmaceutical Co. Ltd., Tokyo, Japan), an oral 5-FU preparation combining tegafur and uracil, with LV (UFT/LV) [6]; however, none of them could show the improvement in overall survival (OS). Nevertheless, because of the high relapse rate even after the curative resection of CLM [7], adjuvant chemotherapy has been widely used in actual clinical settings considering the resected tumor burden or the performance status of patients.

In actual clinical settings, patients who are considered to be at high risk of recurrence can be candidate for adjuvant chemotherapy. Disease-free interval (DFI) from resection of primary lesion can be a factor estimating the risk of recurrence after hepatectomy for CLM [8]. However, definitions of synchronous and metachronous presentation vary among studies [4, 6] and its influence on the efficacy of adjuvant chemotherapy has not well been studied so far.

The objective of this study was to investigate the efficacy of adjuvant chemotherapy for patients undergoing hepatic resection for CLM stratified by chemotherapy regimens and DFI.

Materials and Methods

Study Population

We carried out a search of a prospectively collected database at Toranomon Hospital between January 2008 and June 2016, and identified 227 patients who underwent curative surgical resection for CLM. Of these, 104 patients did not receive any adjuvant therapy and 123 patients received adjuvant chemotherapy after hepatic resection. Forty-seven patients were administered with UFT/LV, 58 patients underwent oxaliplatin-based chemotherapy; 28 patients were given FOLFOX, and 30 were given CapeOX. The remaining 18 patients, who received postoperative chemotherapy in other hospitals (7 patients) or those who received the other agents (capecitabine, $n = 6$; S-1, $n = 2$; irinotecan, $n = 1$; bevacizumab, $n = 1$; panitumumab, $n = 1$) were excluded and 209 patients were finally included in the analysis. All the analyses in the current study were performed in accordance with the ethical guidelines for clinical studies at Toranomon Hospital with the approval of the institutional review board.

The study population was stratified by DFI as follows: synchronous CLM (S-CLM), CLM detected at or before diagnosis of the primary tumor; early metachronous CLM (EM-CLM), EM-CLM with DFI ≤ 1 year; late metachronous CLM (LM-CLM), CLM with DFI > 1 year. Major hepatectomy was defined as hepatic resection 3 or more Couinaud's segments. R0 resection was defined as microscopically negative surgical margins, and R1 resection as very narrow surgical margins (< 1 mm). Major complication was defined as complication classified into grade 3 or more in Clavien-Dindo classification.

Adjuvant Chemotherapy

Adjuvant chemotherapy was started within 3 months after curative hepatic resection. Selection of chemotherapy regimen or initial dose reduction was determined by physician's preference considering the performance status of the patients, resected tumor burden, and patients' request about route of administration.

In patients administered with UFT/LV, UFT (300 mg/m²/day as tegafur) and LV (75 mg/day) were simultaneously administered every day for 6–18 months after surgery as previously described [9]. In patients with oxaliplatin, either FOLFOX4 or FOLFOX6 or CapeOX was used for 6 months, according to a former study [10]. Adjuvant therapy was stopped (1) when recurrence was observed, (2) when a patients developed unmanageable toxicity, or (3) when a patient refused to continue chemotherapy.

The Evaluation of Safety

Adverse events were evaluated according to Common Terminology Criteria for Adverse Events, version 4.0. The worst grade of each adverse event was recorded. The decision to reduce the dose of agents by adverse events was left to each doctor. The relative dose intensity (RDI) of UFT/LV or Oxaliplatin was calculated as follows: RDI = total administered dose divided by the total scheduled dose $\times 100$ (%).

Statistical Analysis

Categorical variables were compared using the χ^2 test or Fisher's exact test and continuous variables were compared using the Kruskal-Wallis or Mann-Whitney U test as appropriate. The OS period and the RFS period were determined from the date of hepatic resection until the date of death or the initial tumor recurrence, respectively. All the cases without specific prognostic events were censored at the date of the last follow-up examination. The survival curves were generated using the Kaplan-Meier method and were compared using a log-rank test.

To investigate the prognostic factors, the influence of 13 items was assessed in univariate analysis using the Cox proportional hazards model: age (≤ 60 or > 60), gender, primary tumor location, primary tumor nodal status, CEA before hepatic surgery (≤ 5 or > 5 ng/mL), CA19-9 before hepatic surgery (≤ 40 or > 40 ng/mL), adjuvant chemotherapy after the primary resection, neoadjuvant chemotherapy before hepatic surgery, number of liver metastases (1, 2–4, 5 $\leq$), tumor size (> 5 or ≤ 5 cm), surgical procedure (major hepatectomy or minor hepatectomy), surgical margin, and the regimen of adjuvant chemotherapy after hepatic surgery. Variables with $p < 0.1$ were included in the Cox multivariate model. $p < 0.05$ was set as indicating a statistically significant difference. Statistical analyses were performed using the JMP software (version 11.0; SAS Institute Inc., USA).

Results

Patient Characteristics

As shown in Table 1, the study cohort included 152 men (72.7%) and 57 women (27.3%), with a median age of 63 years (range 35–88 years). The primary tumor was in the colon in 125 patients (59.8%) and in the rectum in

Table 1. Baseline demographics and clinical characteristics of all patients

	Total (<i>n</i> = 209)		No adjuvant (<i>n</i> = 104)		Adjuvant (<i>n</i> = 105)		<i>p</i> value
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	
Age, years							
Median	63		65		63		0.014
Range	35–88		36–88		35–74		
Gender							
Male	152	72.7	77	74.0	75	71.4	0.672
Female	57	27.3	27	26.0	30	28.6	
Primary tumor							
Colon	125	59.8	64	61.5	61	40.2	0.612
Rectum	84	40.2	40	38.5	44	59.8	
Primary tumor nodal status							
Positive	127	60.8	56	65.4	59	56.2	0.173
Negative	82	39.2	26	34.6	46	43.8	
CEA before hepatic surgery, ng/mL							
Median	6.8		6.4		7		0.297
Range	1.0–1,545		1.0–347		1.1–1,545		
CA19-9 before hepatic surgery, ng/mL							
Median	23.5		22.5		25.5		0.210
Range	0–30,440		0–30,440		0–2,236		
Adjuvant chemotherapy after the primary resection							
Yes	77	36.8	37	35.6	40	38.1	0.706
No	132	63.2	67	64.4	65	61.9	
Neoadjuvant chemotherapy before hepatic surgery							
Yes	49	23.4	24	23.1	25	23.8	0.901
No	160	76.6	80	76.9	80	76.2	
Interval between primary resection and diagnosis of liver metastases							
≤0 (S-CLM)	68	32.5	27	26.0	41	39.1	0.121
0–1 year (EM-CLM)	64	30.6	36	34.6	28	26.7	
>1 year (LM-CLM)	77	36.8	41	39.4	36	34.3	
Number of liver metastases							
1	111	53.1	56	53.9	55	52.4	0.073
2–4	75	35.9	32	46.1	43	41.0	
5≤	23	11.0	16	15.4	7	6.7	
Tumor size before surgery, cm							
Median	2.3		2.4		2.2		0.639
Range	0.6–14		0.7–14		0.6–10		
Hepatectomy							
Major resection	44	21.1	22	21.2	8	18.6	0.966
Minor resection	165	78.9	82	78.8	35	81.4	
Operating time, min							
Median	165		176		163		0.204
Range	47–503		47–503		55–342		
Blood loss, mL							
Median	345		347		340		0.731
Range	0–3,488		0–2,871		0–3,488		
Transfusion	11	5.3	6	5.8	5	4.8	0.732
Surgical margin							
R0	160	76.6	77	74.0	83	79.1	0.392
R1	49	23.4	27	26.0	22	20.9	
Major complication	23	11.0	16	15.4	9	8.6	0.127

Major resection was defined as hepatic resection 3 or more Couinaud's segments.

R0 was defined as microscopically negative surgical margins, and R1 was defined as very narrow surgical margins (<1 mm).

Major complication was defined as complication classified into grade 3 or more in Clavien-Dindo classification.

Fig. 1. Recurrence-free survival (RFS) according to adjuvant chemotherapy stratified by disease-free interval. Recurrence-free survival in patients with (a) synchronous CLM (S-CLM); b early metachronous CLM (EM-CLM); c late metachronous CLM (LM-CLM).

the remaining patients. Lymph node metastases at the time of resection of the primary tumor were observed in 127 patients (60.8%). The median value of CEA before hepatic surgery was 6.8 ng/mL (range 1.0–1,545) and that of CA19–9 before hepatic surgery was 23.5 ng/mL (0–30,440). Seventy-seven patients (36.8%) had a history of adjuvant chemotherapy for primary lesion and 49 patients (23.4%) received preoperative chemotherapy before resection of CLM. Sixty-eight patients (32.5%) had S-CLM, and DFI was within 1 year (EM-CLM) in 64 patients (30.6%) and more than 1 year (LM-CLM) in 77 patients (36.8%). Ninety-eight patients (46.9%) had multiple CLM and the median size of the CLM was 2.3 cm (range 0.6–14). Forty-four patients (21.1%) underwent major hepatectomy, and 23 patients (11.0%) experienced major morbidity. R0 resection were obtained in 160 patients (76.6%), while the other cases exhibited very narrow surgical margins (<1 mm) (R1 resection). There were no patients who underwent staged surgery, ablation therapies, or the other anti-cancer treatment.

When compared to patients with no adjuvant chemotherapy, those who underwent adjuvant chemotherapy tended to be elder (median 65 vs. 63, $p = 0.014$); however, there was no statistical difference in the other profile. The mean observation period was 28 months for patients without adjuvant chemotherapy and 48 months for those who underwent adjuvant chemotherapy ($p < 0.001$), reflecting the decreased rate of adjuvant chemotherapy from 58% before 2014 to 31% after 2015 in the current population due to lack of solid evidence for adjuvant therapy. The number of patients censored was 69 (66.4%) in patients without adjuvant therapy and 71 (67.6%) in those with adjuvant therapy, respectively ($p = 0.845$). The num-

ber of patients lost to follow-up was 9 (8.7%) in patients without adjuvant therapy and 14 (13.3%) in those with adjuvant therapy, respectively ($p = 0.278$).

Feasibility of Adjuvant Chemotherapy

The proportion of patients who completed the scheduled adjuvant chemotherapy was higher in the UFT group (84.1%) than that in the OX group (44.6%; $p < 0.001$), although there was no statistical difference of RFS or OS between patients with/without completion of scheduled adjuvant chemotherapy in both UFT/LV and oxaliplatin-based regimen group. Severe adverse events (grades 3 or 4) were significantly frequent in the OX group (50.9%) compared to the UFT group (6.8%; $p < 0.001$). The RDI was $95.0 \pm 4.1\%$ in the UFT group and $84.8 \pm 5.2\%$ in the OX group ($p = 0.004$), respectively.

Prognostic Factors in Patients with CLM

Figure 1 shows RFS of patients with/without adjuvant chemotherapy stratified by DFI (i.e., S-CLM, EM-CLM, and LM-CLM). Five-year RFS rates were 11.2% in patients with no adjuvant chemotherapy, 32.8% in those with adjuvant chemotherapy ($p = 0.002$) in the S-CLM group, 15.2%, 43.7% ($p = 0.002$) in the EM-CLM group, and 29.6%, 44.1% ($p = 0.163$) in the LM-CLM group, respectively. Figure 2 shows OS and the 5-year OS rates were 44.5% in patients with no adjuvant chemotherapy, 77.9% in those with adjuvant chemotherapy ($p = 0.021$) in the S-CLM group, 39.5%, 81.5% ($p = 0.015$) in the EM-CLM group, and 65.4%, 76.1% ($p = 0.411$) in the LM-CLM group, respectively.

Subsequently, in S-CLM and EM-CLM (i.e., DFI ≤ 1 year), multivariate analyses of factors associated with

Fig. 2. Overall survival (OS) according to adjuvant chemotherapy stratified by disease-free interval. OS in patients with **(a)** synchronous CLM (S-CLM); **(b)** early metachronous CLM (EM-CLM); **(c)** late metachronous CLM (LM-CLM).

long-term outcomes was performed (Tables 2, 3). As for RFS, R0 resection (HR 0.439; 95% CI 0.257–0.772; $p = 0.005$), and adjuvant chemotherapy after hepatectomy (UFT/LV vs. none, HR 0.385; 95% CI 0.190–0.725; $p = 0.003$, oxaliplatin vs. none, HR 0.320; 95% CI 0.181–0.549; $p < 0.001$) were significantly correlated with better RFS. Regarding the prognostic factors for OS, the same 2 factors were found to be associated with better OS: R0 resection (HR 0.299; 95% CI 0.048–0.999; $p = 0.050$), and adjuvant chemotherapy after hepatectomy (UFT/LV vs. none, HR 0.269; 95% CI 0.086–0.696; $p = 0.006$, oxaliplatin vs. none, HR 0.286 95% CI 0.109–0.670; $p = 0.003$).

As for the regimen of adjuvant chemotherapy in CLM with DFI ≤ 1 year, RFS and OS in patients who received UFT/LV or oxaliplatin-based regimen are shown in Figure 3. In patients with DFI ≤ 1 year, patients who underwent adjuvant chemotherapy showed significantly better RFS and OS regardless of the regimen than those with no adjuvant chemotherapy and there was no difference in both RFS and OS between the UFT/LV group and oxaliplatin-based regimen (regarding RFS, UFT/LV vs. none, $p = 0.002$; oxaliplatin vs. none, $p < 0.001$; UFT/LV vs. oxaliplatin, $p = 0.942$; regarding OS, UFT/LV vs. none, $p = 0.008$; oxaliplatin vs. none, $p = 0.003$; UFT/LV vs. oxaliplatin, $p = 0.918$).

Discussion

In this study, we evaluated the prognostic impact of adjuvant chemotherapy using UFT/LV or oxaliplatin after curative hepatic resection for CLM stratified by DFI. Adjuvant chemotherapy prolonged both RFS and OS in

CLM with DFI ≤ 1 year, and both UFT/LV and oxaliplatin had the effect on improving prognosis to the same degree. However, no prognostic advantage of adjuvant chemotherapy was confirmed in CLM with DFI > 1 year. UFT/LV was associated with a lower abandon rate and lower adverse effect compared with oxaliplatin-based regimens followed during adjuvant systemic therapy.

It has been reported that hepatic resection significantly improves the outcome of patients with CLMs; however, recurrence occurs in 70–80% of them [7, 11]. Although S-CLM is well known to have less favorable prognosis [12], DFI ≤ 1 year is also reported to be a risk factor for poor prognosis and EGOSLIM group classified metachronous CLM with DFI ≤ 1 year into EM-CLM and the others into LM-CLM [8].

In patients with stages II or III CRC, adjuvant chemotherapy using UFT/LV [9, 13] or oxaliplatin [14, 15] has been validated to prolong RFS and OS. However, there is only less evidence on the adjuvant chemotherapy for patients with CLM [5], though both UFT/LV and oxaliplatin have been reported to be feasible in adjuvant settings after hepatic resection [10, 16].

UFT is an oral 5-FU prodrug and UFT/LV therapy has been reported to be not inferior to 5-FU/LV as adjuvant chemotherapy for stages II or III CRC [13]. It has also been confirmed that adjuvant chemotherapy using oxaliplatin-based regimen may achieve better RFS and OS than 5-FU/LV alone among patients with stages II or III CRC [14, 15]. However, specific adverse events such as neutropenia or sinusoidal injury in the liver might limit the prolonged use of oxaliplatin. In a previous study, the completion rate of postoperative FOLFOX in adjuvant settings was 44% and grades 3 or 4 adverse

Table 2. Multivariate analysis of RFS in patients with DFI ≤1 year liver metastases

	Number of patients	Five-year RFS, %	Univariate analysis			Multivariate analysis		
			<i>p</i> value	HR	95% CI	<i>p</i> value	HR	95% CI
Age, years								
>60	82	30.3	0.140	0.719	0.467–1.117			
≤60	50	19.8						
Gender								
Male	92	30.8	0.197	0.741	0.476–1.174			
Female	40	17.2						
Primary tumor								
Rectum	47	30.3	0.707	0.918	0.582–1.425			
Colon	85	23.3						
Primary tumor nodal status								
Negative	47	34.2	0.339	0.801	0.499–1.256			
Positive	85	25.9						
CEA before surgery, ng/mL								
≤5	51	34.8	0.177	0.737	0.465–1.145			
>5	82	21.3						
CA19-9 before surgery, ng/mL								
≤40	76	33.3	0.209	0.737	0.465–1.145			
>40	56	18.5						
Adjuvant chemotherapy after the primary resection								
Yes	92	34.6	0.513	0.854	0.521–1.358			
No	40	20.8						
Neoadjuvant chemotherapy before hepatic surgery								
No	92	31.7	0.094	0.675	0.433–1.071	0.437	0.814	0.490–1.376
Yes	40	11.6						
Hepatectomy								
Minor resection	96	23.5	0.321	0.782	0.491–1.284			
Major resection	36	30.7						
Number of liver metastases								
1	55	41.7	<0.001	0.281	0.153–0.531	0.082	0.511	0.248–1.091
2–4	57	43.2	0.025	0.496	0.281–0.911	0.878	0.948	0.490–1.908
≤5	20	15.2						
Tumor size, cm								
≤5	119	90.2	0.142	0.588	0.318–1.216			
>5	13	9.8						
Surgical margin								
R0	107	32.3	0.010	0.504	0.314–0.839	0.005	0.439	0.257–0.772
R1	25	10.7						
Adjuvant chemotherapy								
None	63	13.1	0.002	0.389	0.196–0.713	0.003	0.385	0.190–0.725
Adjuvant with UFT/LV	25	41.6						
Adjuvant with oxaliplatin	44	37.2	<0.001	0.399	0.239–0.651	<0.001	0.320	0.181–0.549

CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9.

events were more frequent than the preoperative period [4]. In contrast, it has been reported that UFT/LV is associated with a better continuation rate and milder adverse events [16], and the current results also confirmed that UFT/LV was associated with a better continuation

rate and lower adverse events compared with oxaliplatin-based regimen.

There were 2 noteworthy results in this study. First, adjuvant chemotherapy may be associated with better RFS and OS not only in S-CLM but also in EM-CLM.

Table 3. Multivariate analysis of OS in patients with DFI ≤1 year liver metastases

	Number of patients	Five-year OS, %	Univariate analysis			Multivariate analysis		
			<i>p</i> value	HR	95% CI	<i>p</i> value	HR	95% CI
Age, years								
>60	82	63.8	0.956	0.979	0.480–2.078			
≤60	50	64.7						
Gender								
Male	92	64.4	0.799	0.906	0.437–2.012			
Female	40	63.8						
Primary tumor								
Colon	85	63.4	0.704	0.872	0.428–1.784			
Rectum	47	63.9						
Primary tumor nodal status								
Positive	85	68.2	0.826	0.920	0.448–1.992			
Negative	47	57.8						
CEA before surgery, ng/mL								
≤5	51	71.4	0.132	0.562	0.245–1.183			
>5	82	59.3						
CA19-9 before surgery, ng/mL								
>40	56	69.7	0.198	0.627	0.306–1.281			
≤40	76	56.7						
Adjuvant chemotherapy after the primary resection								
Yes	92	64.3	0.850	1.074	0.428–1.920			
No	40	64.8						
Neoadjuvant chemotherapy before hepatic surgery								
Yes	40	71.5	0.571	0.795	0.333–1.708			
No	92	60.8						
Hepatectomy								
Minor resection	96	64.6	0.516	0.775	0.373–1.724			
Major resection	36	61.4						
Number of liver metastases								
1	55	41.7	0.165	0.410	0.135–1.510			
2–4	57	43.2						
≤5	20	15.2	0.862	0.906	0.332–3.169			
Tumor size, cm								
≤5	119	90.2	0.283	0.571	0.238–1.692			
>5	13	9.8						
Surgical margin								
R0	107	89.7	0.041	0.289	0.047–0.959	0.050	0.299	0.048–0.999
R1	25	59.1						
Adjuvant chemotherapy								
None	63	40.2	0.008	0.283	0.091–0.732	0.006	0.269	0.086–0.696
Adjuvant with UFT/LV	25	89.2						
Adjuvant with oxaliplatin	44	72.8	0.002	0.267	0.101–0.627	0.003	0.286	0.109–0.670

CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9.

Conventionally, it has been reported that perioperative chemotherapy may not benefit patients with EM-CLM [17]; however, the present analysis showed that adjuvant therapy may be advantageous also for EM-CLM. Prognostic superiority of EM-CLM would be attribut-

able to the longer observational period from the diagnosis of primary lesion, which might be associated with a reduced risk of occult lesion in the liver. Given that the purpose of adjuvant chemotherapy is to expect eradication of occult lesions remaining in the liver, the current

Fig. 3. Surgical outcome according to the regimen of adjuvant chemotherapy in patients with DFI ≤ 1 year. Recurrence-free survival (a) and overall survival (b) in patients with DFI ≤ 1 year (i.e., synchronous CLM and early metachronous CLM).

observation suggests that EM-CLM remains harboring a higher risk of latent metastatic lesions compared to LM-CLM. Therefore, EM-CLM can be a candidate for adjuvant therapy after curative resection. Second, patients who received UFT/LV showed outcomes similar to those who underwent oxaliplatin-based regimens after curative resection. Although it is difficult to conclude that UFT/LV may have equivalent efficacy compared to the oxaliplatin-based regimens, one of the advantages of UFT/LV would be lower toxicity in comparison with standard cytotoxic regimens. Hepatic resection is generally an invasive procedure, and accordingly, it is not always feasible to complete the doublet cytotoxic regimen such as FOLFOX or FOLFIRI due to decreased performance status and delayed recovery from surgery as reported in EORTC 40983 [4]. However, as indicated in this study, UFT/LV can be administered at a higher dose intensity and with a higher completion rate. Therefore, UFT/LV could be a choice of adjuvant chemotherapy after curative surgical resection of CLM, especially for elderly patients or those with poor performance status after surgery.

The limitations of this study include its retrospective nature, limited number of subjects and ambiguity in selecting the regimen. However, the present analysis was based on a prospectively collected database, and it is im-

portant that the current study suggested potential prognostic advantage of adjuvant chemotherapy for patients with CLM with DFI of less than 1 year. External validation using a larger population with adequate statistical methods (e.g., propensity-score adjustment analysis) would be needed to confirm the present results, and the current results may warrant randomized controlled trial comparing UFT/LV and FOLFOX as adjuvant therapy for CLM.

In conclusion, adjuvant chemotherapy using either UFT/LV or oxaliplatin may improve the long-term outcomes after surgery not only in patients with synchronous but also EM-CLM with DFI ≤ 1 year. In adjuvant therapy after hepatic resection, UFT/LV might be a choice of regimen considering its safety and higher feasibility.

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Disclosure Statement

Authors have no conflicts of interest to disclose.

References

- Cummings LC, Payes JD, Cooper GS: Survival after hepatic resection in metastatic colorectal cancer: a population-based study. *Cancer* 2007;109:718–726.
- Adam R, De Gramont A, Figueras J, Guthrie A, Kokudo N, Kunstlinger F, Loyer E, Poston G, Rougier P, Rubbia-Brandt L, Sobrero A, Tabernero J, Teh C, Van Cutsem E, Jean-Nicolas Vauthey of the EGOSLIM (Expert Group on OncoSurgery management of Liver Metastases) Group: The oncosurgery approach to managing liver metastases from colorectal cancer: a multidisciplinary international consensus. *Oncologist* 2012;17:1225–1239.
- Shindoh J, Loyer EM, Kopetz S, Boonsirikamchai P, Maru DM, Chun YS, Zimmitti G, Curley SA, Charnsangavej C, Aloia TA, Vauthey JN: Optimal morphologic response to preoperative chemotherapy: an alternate outcome end point before resection of hepatic colorectal metastases. *J Clin Oncol* 2012;30:4566–4572.
- Nordlinger B, Sorbye H, Glimelius B, Poston GJ, Schlag PM, Rougier P, Bechstein WO, Primrose JN, Walpole ET, Finch-Jones M, Jaeck D, Mirza D, Parks RW, Collette L, Praet M, Bethe U, Van Cutsem E, Scheithauer W, Gruenberger T: Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. *Lancet* 2008;371:1007–1016.
- Portier G, Elias D, Bouche O, Rougier P, Bosset JF, Saric J, Belghiti J, Piedbois P, Guimbaud R, Nordlinger B, Bugat R, Lazorthes F, Bedenne L: Multicenter randomized trial of adjuvant fluorouracil and folinic acid compared with surgery alone after resection of colorectal liver metastases: FFCD ACHBTH AURC 9002 trial. *J Clin Oncol* 2006;24:4976–4982.
- Hasegawa K, Saiura A, Takayama T, Miyagawa S, Yamamoto J, Ijichi M, Teruya M, Yoshimi F, Kawasaki S, Koyama H, Oba M, Takahashi M, Mizunuma N, Matsuyama Y, Watanabe T, Makuuchi M, Kokudo N: Adjuvant oral uracil-tegafur with leucovorin for colorectal cancer liver metastases: a randomized controlled trial. *PLoS One* 2016;11: e0162400.
- Tomlinson JS, Jarnagin WR, DeMatteo RP, Fong Y, Kornprat P, Gonen M, Kemeny N, Brennan MF, Blumgart LH, D'Angelica M: Actual 10-year survival after resection of colorectal liver metastases defines cure. *J Clin Oncol* 2007;25:4575–4580.
- Adam R, de Gramont A, Figueras J, Kokudo N, Kunstlinger F, Loyer E, Poston G, Rougier P, Rubbia-Brandt L, Sobrero A, Teh C, Tejpar S, Van Cutsem E, Vauthey JN, Pahlman L: Managing synchronous liver metastases from colorectal cancer: a multidisciplinary international consensus. *Cancer Treat Rev* 2015;41: 729–741.
- Sadahiyo S, Tsuchiya T, Sasaki K, Kondo K, Katsumata K, Nishimura G, Kakeji Y, Baba H, Sato S, Koda K, Yamaguchi Y, Morita T, Matsuo K, Usuki H, Hamada C, Kodaira S: Randomized phase III trial of treatment duration for oral uracil and tegafur plus leucovorin as adjuvant chemotherapy for patients with stage IIB/III colon cancer: final results of JFMC33–0502. *Ann Oncol* 2015;26:2274–2280.
- Nakayama I, Suenaga M, Wakatsuki T, Ichimura T, Ozaka M, Takahari D, Shinozaki E, Chin K, Ueno M, Mizunuma N, Yamaguchi T: Safety, tolerability, and efficacy of oxaliplatin-based adjuvant chemotherapy after curative resection of hepatic or extrahepatic metastases of stage IV colorectal cancer. *Cancer Chemother Pharmacol* 2015;76:133–139.
- Jones RP, Jackson R, Dunne DF, Malik HZ, Fenwick SW, Poston GJ, Ghaneh P: Systematic review and meta-analysis of follow-up after hepatectomy for colorectal liver metastases. *Br J Surg* 2012;99:477–486.
- Nordlinger B, Guiguet M, Vaillant JC, Balladur P, Boudjema K, Bachellier P, Jaeck D: Surgical resection of colorectal carcinoma metastases to the liver. A prognostic scoring system to improve case selection, based on 1568 patients. *Association Française de Chirurgie. Cancer* 1996;77:1254–1262.
- Lembersky BC, Wieand HS, Petrelli NJ, O'Connell MJ, Colangelo LH, Smith RE, Seay TE, Giguere JK, Marshall ME, Jacobs AD, Colman LK, Soran A, Yothers G, Wolmark N: Oral uracil and tegafur plus leucovorin compared with intravenous fluorouracil and leucovorin in stage II and III carcinoma of the colon: results from National Surgical Adjuvant Breast and Bowel Project Protocol C-06. *J Clin Oncol* 2006;24:2059–2064.
- Schmoll HJ, Cartwright T, Tabernero J, Nowacki MP, Figer A, Maroun J, Price T, Lim R, Van Cutsem E, Park YS, McKendrick J, Topham C, Soler-Gonzalez G, de Braud F, Hill M, Sirzen F, Haller DG: Phase III trial of capecitabine plus oxaliplatin as adjuvant therapy for stage III colon cancer: a planned safety analysis in 1,864 patients. *J Clin Oncol* 2007;25:102–109.
- Andre T, Boni C, Navarro M, Tabernero J, Hickish T, Topham C, Bonetti A, Clingan P, Bridgewater J, Rivera F, de Gramont A: Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. *J Clin Oncol* 2009;27:3109–3116.
- Saiura A, Yamamoto J, Hasegawa K, Oba M, Takayama T, Miyagawa S, Ijichi M, Teruya M, Yoshimi F, Kawasaki S, Koyama H, Makuuchi M, Kokudo N: A combination of oral uracil-tegafur plus leucovorin (UFT + LV) is a safe regimen for adjuvant chemotherapy after hepatectomy in patients with colorectal cancer: safety report of the UFT/LV study. *Drug Discov Ther* 2014;8:48–56.
- Adam R, Bhangu P, Poston G, Mirza D, Nuzzo G, Barroso E, Ijzermans J, Hubert C, Ruers T, Capussotti L, Ouellet JF, Laurent C, Cugat E, Colombo PE, Milicevic M: Is perioperative chemotherapy useful for solitary, metachronous, colorectal liver metastases? *Ann Surg* 2010;252:774–787.